A GENETIC ANALYSIS OF THYROXINE-BINDING GLOBULIN VARIANTS IN MAN*

by

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A Thesis

Presented to the Department of Medical Genetics and the Graduate School of Indiana University as partial fulfillment of the requirements for the degree of

Doctor of Philosophy

September, 1969

* This investigation is supported in part by USPHS Grants DE119, FR162, by the Graduate School, Indiana University and by the James Whitcomb Riley Memorial Association.

**Traineeship - USPHS Genetics Training Grant DE119.

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ABSTRACT

Age and sex-related differences in peripheral thyroid indices including PBI, T_3 and T_4 resin uptake, free serum thyroxine, percent endogenous distribution of thyroxine with thyroxine-binding globulin (TBG) and thyroxine-binding pre-albumin (TBPA) and the binding capacities of TBG and TBPA were studied in 337 children and 336 adults.

The values of PBI and T_4 resin uptake in our normal population were independent of age and comparison of the means in the sexes revealed no significant differences. Significant differences were observed in males and females in the 12-13 and 60-69 year old age groups for T_3 resin uptake. Polynomial equations of the fourth degree best described the functional relationship with age of the endogenous distribution of T_4 with TBG and TBPA. Significantly different age distributions were observed for males and females. The relative distribution of thyroxine with each of these proteins also seems to be age-dependent. As the percent of T_4 bound to TBPA increases in an age span, there is a concomitant decrease in the percent bound to TBG; the converse is also true. A quadratic equation best describes the distribution with age of TBPA binding capacity. Significant differences were noted for male and female distributions. Sex and age-related differences were also observed for TBG binding capacity. A positive linear regression with age is observed in females whereas in males, the values remain constant throughout life. The normal range for males is 14.0 - 29.6 ug T_4/100 ml. and the normal range for females varies with age.

The genetic transmission of TBG binding capacity was demonstrated in five families which were ascertained through individuals who participated in our control studies. A new X-linked dominant variant of TBG binding capacity deficiency was found in two of our families. TBG binding capacity values ranged from 3.1 to 3.6 in hemizygous affected males and from 8.9 to 13.4 ug T_4/100 ml. in heterozygous females. The variant gene segregating in these families may be allelic to the gene for absent TBG binding capacity reported by other authors. An autosomal dominant variant of decreased TBG binding capacity was demonstrated in two families. TBG binding capacity values ranged from 9.4 to 14.6 ug T_4/100 ml. in affected individuals. Non-penetrance of the trait was observed in one of these families. Although the results of linkage analysis are inconclusive, there is some suggestion of linkage between the autosomal locus for TBG and the Rh locus. Linkage studies with Xga in our X-linked families were not informative.

TBG binding capacity and other peripheral thyroid indices were measured in several individuals with chromosomal aberrations including G/G, D/G and D/D translocations. The laboratory findings were all within normal limits.

Of the 253 individuals tested for TBG binding capacity, 12 had values between 7.5 and 15.0 ug T_4/100 ml. and 3 had values above 30 ug T_4/100 ml. The incidence of "intermediate" TBG binding capa-

cities in our random sample is 4.7 percent. However, there is a significant difference between the incidence in males and females. 8.7 percent of the males and only 0.7 percent of the females had decreased TBG binding. Higher endogenous levels of estrogen in females may be responsible for the low incidence.

Stepwise regression was used to determine whether PBI, T_3 and T_4 resin uptake, free serum thyroxine levels or combinations thereof would be of use in predicting TBG binding capacity deficiency without its actual measurement by reverse-flow electrophoresis. The ratios T_3/PBI and T_4/PBI contributed to most of the variation between individuals with X-linked decreased TBG binding capacity and those with normal binding levels.

Genetic models based on single factor inheritance adequately explain the strikingly different TBG binding phenotypes observed in our two X-linked families. However, single-factor inheritance cannot explain the wide variation observed in the majority of individuals in our control population or the phenomenon of non-penetrance observed in one of our families. TBG binding capacity may be a polygenic trait with many loci contributing to the observed phenotype.